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Incretin-based pharmacotherapy in the obesity phenotype of heart failure with preserved ejection fraction - Pathophysiology and clinical evidence

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ABSTRACT

Introduction: The most common form of heart failure encountered in clinical practice is heart failure with preserved ejection fraction (HFpEF). It usually affects patients who are overweight. There is an association between increased epicardial and visceral fat and chronic inflammation, microvascular dysfunction, and impaired relaxation of the heart chambers. This review aimed to explore GLP-1 receptor agonists (GLP-1 RA) and dual incretin agonists (GIP/GLP-1 RA) - tirzepatide, in patients with HFpEF and obesity. *Methods*: In this review, we have examined current literature on GLP 1 RA (like semaglutide and GIP/GLP 1 receptor agonists in patients with HFpEF associated with obesity. We concentrated primarily on large-scale randomized trials (STEP HFpEF, STEP-HFpEF DM, SUMMIT). To illustrate the effects of these therapies on clinical outcomes, biomarkers, and epicardial fat, additional imaging and mechanistic work were taken into account. *Results and Discussion*: The findings show that incretin drugs help patients with HFpEF and obesity lose a meaningful amount of weight. Moreover, they lower NT proBNP levels, reduce inflammation, and improve patient functioning. With tirzepatide, the SUMMIT trial reported fewer cardiovascular deaths or worsening heart failure episodes and a decline in epicardial fat volume on cardiac MRI. We conclude that adding incretin therapy to standard treatment is a promising way to ease symptoms in patients with HFpEF and obesity.

Keywords: HFpEF, GLP-1 agonist, tirzepatide, semaglutide, epicardial adipose tissue

1. INTRODUCTION

Older people and those with metabolic comorbidities often experience complications of the most common form of heart failure - with preserved ejection fraction (HFpEF) (El Hadj Othmane et al., 2025; Gil Millán et al., 2025). Obesity

prevalence is rising worldwide, and it is correlated with an increase in HFpEF. Adiposity was considered for a long time just as a comorbidity that increases hemodynamic load. It expands blood volume and raises intrathoracic pressure.

In recent years, this perspective has changed. Different data from trial programs, above all STEP-HFpEF, have established obesity as a contributor to a distinct phenotype rather than a simple co-existing condition (Kosiborod et al., 2023a; Butler et al., 2022; El Hadj Othmane et al., 2025). Recognition of this phenotype has opened new therapeutic options. These go beyond standard diuretic and neurohormonal blockade strategies.

Especially epicardial and pericardial ectopic adipose depots are associated with myocardial injury. Due to local inflammatory activity, they cause microvascular dysfunction and fibrosis of the heart muscle (Verma et al., 2024; Packer et al., 2025). It translates into clinical presentation. Patients with obesity-related HFpEF often report exertional dyspnoea and reduced exercise tolerance despite preserved ejection fraction. The problem does not concern systolic function, but impaired myocardial relaxation, as it becomes stiff and fibrotic. These patients also differ from patients with HFpEF related to hypertension and aging. Usually, they have more resistance in the peripheral and pulmonary arteries, higher pressures in the ventricles at rest and during exercise, and sodium retention due to RAAS activation. In this type, the additional volume is more pronounced than the stiffness and alterations in the heart muscle seen in people with hypertension.

This paradox seems less pronounced when central adiposity is taken into account. Interventions that reduce adiposity and improve its inflammatory and metabolic profile have better clinical outcomes in patients with HFpEF and obesity (Hullon et al., 2025; Borlaug et al., 2025; Zile et al., 2025). These observations support a role for adipose tissue. However, causal inference is still difficult, and the effects of weight loss on weakened or sarcopenic individuals need to be evaluated.

As a result of identifying obesity-related HFpEF, therapeutic strategies have changed. Initially, the role of lifestyle modification and weight-loss diets was emphasized. Unfortunately, weight loss alone produced variable hard endpoints and only modest improvement in cardiac structure (Peck et al., 2024). This is probably due to loss of LBM during weight-loss dieting and to the limited ability to reverse chronic neurohormonal activation and low-grade inflammation (Vest et al., 2024). These limitations have increased interest in pharmacological therapies that can more directly affect body weight, adipose tissue, and inflammatory pathways.

Currently available SGLT2 inhibitors are the main drug group used. They are used across different types of heart failure and reduce the risk of hospitalization (McDonagh et al., 2023; Anker et al., 2021). Used as monotherapy, they usually do not relieve severe exercise limitation in patients with obesity and HFpEF (Cimino et al., 2024). These drugs cause glucosuria and mild natriuresis, which reduces circulating blood volume and preload (Anker et al., 2021). However, weight loss is minimal (Cimino et al., 2024). They also have a very limited effect on visceral and epicardial adipose tissue and on inflammation. Many patients experience symptom relief because congestion decreases, but the mechanical and metabolic stress on the heart and muscles is still present.

Loop diuretics, mainly furosemide and torasemide, are used in heart failure primarily to provide rapid relief of congestion symptoms such as edema and dyspnoea. They strongly increase sodium and water excretion, but they also have clear limitations. Higher doses cause rapid changes in intravascular volume. Patients with heart failure often have stiff, concentrically remodeled ventricles. A sudden drop in preload may lead to acute renal ischemia. This can activate the renin–angiotensin–aldosterone system and the sympathetic nervous system (SNS), which in turn causes vasoconstriction, fluid and salt retention, and recurrent congestion (Reddy et al., 2020). Therefore, GLP-1 receptor agonists such as semaglutide and dual GIP/GLP-1 agonists such as tirzepatide are of interest. They were developed for the treatment of type 2 diabetes and obesity, but it has been proven that they show beneficial cardiovascular effects. In addition, they have a protective effect on the kidneys and the myocardium, and support weight loss (Kosiborod et al., 2023b; Zile et al., 2025).

2. REVIEW METHODS

We carried out a narrative literature review to assess incretin-based pharmacotherapy in HFpEF and obese individuals. Using combinations of the English-language phrases "heart failure with preserved ejection fraction", "HFpEF", "obesity", "epicardial adipose tissue", "GLP-1 receptor agonist", "semaglutide", "tirzepatide", "GIP/GLP-1 agonist", and "twincretin", PubMed/MEDLINE, Scopus, and Google Scholar were searched up to 31 March 2026. Reference lists of important original studies and large meta-analyses were manually examined to find more publications.

We Included randomised controlled trials of GLP-1 receptor agonists or dual GIP/GLP-1 agonists in individuals with HFpEF and obesity (e.g., STEP-HFpEF, STEP-HFpEF DM, SUMMIT), prespecified post hoc or pooled analyses from these programmes, systematic reviews and meta-analyses in HFpEF or HFmrEF/HFpEF populations, observational cohort studies with cardiovascular endpoints, and

mechanistic or translational investigations (echocardiography, cardiac MRI, haemodynamics, proteomics) evaluating the impact of incretin treatment on cardiac structure, epicardial adipose tissue, haemodynamics, endothelial function, or inflammatory markers.

Abstracts lacking the full text as well as sources that have not undergone peer review were excluded. Initially, the literature search was focused on English-language literature published from January 2022 to March 2026. Important studies before this time period on the pathophysiology of HFpEF and the interplay of the heart and kidney relationship were considered based on their citation in the papers selected. Because of the differences in study designs, patient demographics, and outcome measures, an official quantitative meta-analysis was not carried out. Data were instead combined quantitatively with special attention to major randomized studies and premium systematic reviews. Interpretation of outcomes took into account endpoint choice, risk of bias, and the degree to which study populations matched everyday clinical HFpEF practice. Altogether, 62 full text articles that met the inclusion criteria were retrieved and analyzed in this review, as shown in the PRISMA flow diagram (Figure 1).

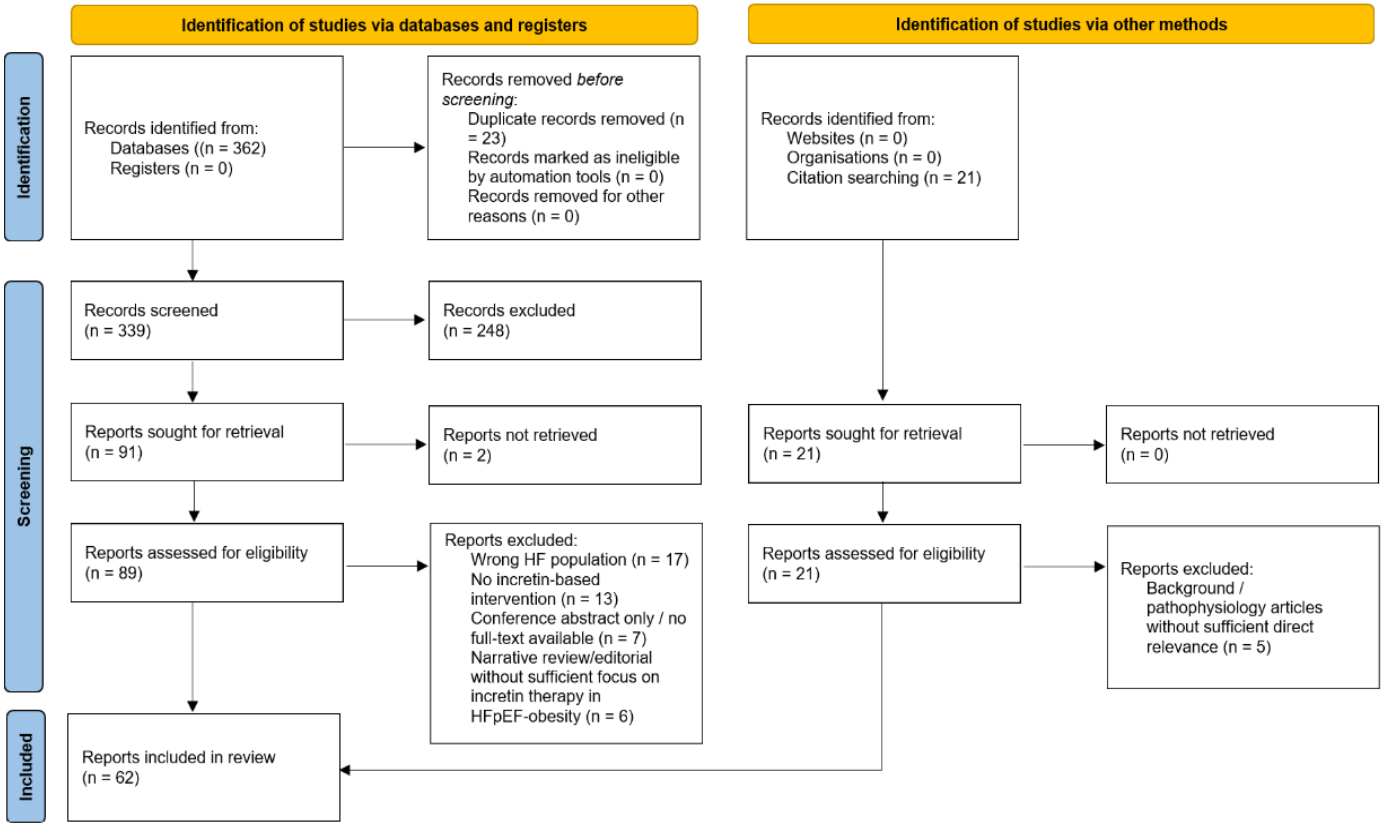

Figure 1. PRISMA flow chart

3. RESULTS AND DISCUSSION

Pathophysiology

The consequence of excess adipose tissue is activation of the immune system and impairment of endothelial function. This is also reported by the EXSCEL study and other proteomic studies conducted in obese patients with HFpEF and metabolic disturbances (Peters et al., 2025; Verma et al., 2024). The whole process begins with low-grade inflammation that accompanies obesity. Continuous excessive caloric intake leads to hypertrophy of visceral adipocytes. This leads to failure of their microcirculation and hypoxia. Too little oxygen causes the release of factors attracting macrophages, and their polarization toward the pro-inflammatory M1 phenotype follows. Remodeled adipose tissue releases more cytokines, including leptin, TNF, and IL-6. Simultaneously, levels of the defensive adiponectin drop (Thomas et al., 2026; Verma et al., 2024). This kind of situation encourages damage and remodeling of the endothelial tissue. The epicardial adipose tissue (EAT), which lies directly adjacent to the myocardium, does not have a separating fascia. It releases inflammatory mediators that therefore act via paracrine signaling on the cardiac microcirculation and expose the coronary endothelium. Intracellular oxidative stress and the expression of adhesion molecules increase. Reactive oxygen species damage

endothelial nitric oxide synthase, thereby decreasing the synthesis and bioavailability of nitric oxide (Paulus & Tschöpe, 2013; Verma et al., 2024).

Nitric oxide deficiency in the coronary circulation impairs activation of the soluble guanylate cyclase (sGC) pathway in cardiomyocytes. The intracellular concentration of cGMP decreases, and this limits the activity of protein kinase G (PKG). This kinase ensures proper phosphorylation of titin, the giant sarcomeric protein. Thanks to it, the chambers of the heart muscle are elastic. Disruption of signaling along this pathway leads to decreased phosphorylation of titin's N2B segment, resulting in increased stiffness of the left ventricular wall (Cai et al., 2023; Verma et al., 2024). At the same time, signals from the epicardial adipose tissue stimulate the activity of myofibroblasts. Excessive collagen production occurs, which is then deposited as a rigid extracellular matrix. This subsequently results in ongoing interstitial fibrosis (Packer et al., 2025).

How incretin drugs work at the molecular and cellular level

GLP-1 receptor agonists not only improve congestion symptoms by reducing body weight and lowering volume overload. They exert an effect on the pathophysiological pathways in obesity-related HFpEF. Studies have shown that GLP-1 receptors (GLP-1 R) are located on the surface of, among others, endothelial cells, smooth muscle cells, macrophages, and the atria of the heart (Roy et al., 2026). As a result of their activation, a signaling cascade is initiated.

It should be noted that the effect of GLP-1 receptor agonists on eNOS and NO restoration to normal production levels is especially important. As the bioavailability of nitric oxide increases, the cGMP-PKG signaling pathway becomes activated. The proper phosphorylation of T2B titin isomers occurs. It results in the decreased stiffness and resting tension of the muscle fibers of the heart (Roy et al., 2026; Thomas et al., 2026).

One further advantage of GLP-1 agonists is their capacity to fight fibrosis and inflammation. They block the creation of the NLRP3 inflammasome inside macrophages, attacking the fat tissue surrounding the heart. This action restricts the conversion of pro-IL-1β and the discharge of IL-1β. Thus, the amounts of pro-inflammatory cytokines inside the microenvironment of the heart decrease. Inhibition of fibroblast proliferation and collagen synthesis leads to increased compliance of the heart muscle (Michos et al., 2023; Thomas et al., 2026). The metabolic effects of GLP-1 receptor agonists may be explained by the activation of PKA and AMPK, resulting in translocation of the glucose transporter type 4 (GLUT4) to the membrane of cells. Thus, there is an increase in glucose consumption and ATP synthesis with reduced oxygen consumption. As a result, the tolerance of ischemia by the myocardium improves (Roy et al., 2026; Thomas et al., 2026). GLP-1 agonists also exert their beneficial effect on the kidneys. In the proximal tubule, these drugs inhibit sodium-hydrogen exchanger type 3 (NHE3). Its effects include higher sodium excretion and a slight osmotic diuresis. There is also no involvement of the renin-angiotensin-aldosterone system in reducing the preload. There is also vasodilation and renal protection (Mann et al., 2021; Michos et al., 2023).

Evidence from STEP-HFpEF trials

Once weekly, semaglutide at a dose of 2.4 mg was examined in the STEP-HFpEF program for its effects on symptoms and quality of life in patients with obesity and HFpEF but without diabetes. These multicentre trials deliberately focused on patients with the typical obesity phenotype of HFpEF and excluded those with reduced ejection fraction, which allowed the effects of therapy to be assessed more precisely in this specific population (Kosiborod et al., 2023b).

The study included 529 non-diabetic participants with a body mass index (BMI) of at least 30 kg/m² (Kosiborod et al., 2023a). After 52 weeks, the main objectives were defined as the percentage decrease in body weight and the change in the clinical summary score of the Kansas City Cardiomyopathy Questionnaire (KCCQ-CSS). In comparison to the placebo group's 8.7 points, the patients taking semaglutide scored 16.6 points higher on the KCCQ-CSS, on average. The difference between the groups was 7.8 points (95% CI 4.8–10.9; $p < 0.001$). Weight reduction was greater in the semaglutide group and amounted to 13.3% on average, whereas among participants receiving a placebo, it was 2.6%. This gives a difference of 10.7 percentage points (95% CI -11.9 to -9.4; $p < 0.001$). An improvement in exercise capacity measured by the 6-minute walk distance (6MWD) was also observed, and it improved on average by 21.5 meters in the semaglutide group compared with 1.2 meters in the placebo group ($p < 0.001$) (Kosiborod et al., 2023a). This result in KCCQ-CSS exceeds the threshold of clinical significance in cardiology (generally, about 5 points is accepted).

The STEP HFpEF DM study enrolled 616 individuals who had both obesity and type 2 diabetes. In them, the placebo group had a mean KCCQ-CSS score improvement of 6.4 points, whereas the semaglutide group had a mean KCCQ-CSS score improvement of 13.7 points. In this study, weight loss was less noticeable. Still, Borlaug et al., (2025b) discovered a statistically significant difference between

the two groups. Based on the study of this initiative, weight reduction alone contributed roughly 40% of the increase in KCCQ-CSS and 6MWD. This shows that semaglutide's benefits go beyond only weight loss (Musa et al., 2026; Thomas et al., 2026).

When data from both STEP HFpEF trials were combined, giving a total of 1,145 patients, semaglutide treatment was associated with fewer heart hospitalizations due to heart failure and a reduced need to escalate loop diuretic doses. A greater proportion of patients receiving semaglutide were able to safely reduce their diuretic dose or stop diuretics altogether (Butler et al., 2024; Patel et al., 2024). Subgroup analyses demonstrated that the efficacy of semaglutide was independent of age. Of particular note, patients who met frailty criteria not only tolerated the treatment well but actually derived the largest absolute improvements in KCCQ CSS and 6-minute walk distance (Pandey et al., 2025).

Changes in cardiac structure, imaging, and biomarkers

The diagnostic challenge in obese patients, due to the so-called natriuretic peptide paradox, is the evaluation of hemodynamic overload. Greater amounts of adipose tissue cause an increase in the expression of NPR-C receptors. There is an acceleration of NT-proBNP clearance and a possible decrease in its concentration (El Hadj Othmane et al., 2025). The results of the STEP-HFpEF study, despite this masking effect, showed that after one year of semaglutide treatment, a greater decrease in NT-proBNP concentration was observed in obese patients (on average, -22.19%) compared with those receiving placebo (-4.87%). This yields a treatment ratio of 0.82 (95% CI 0.74–0.91; $p < 0.001$). This is evidence of a real reduction in left ventricular wall stress and filling pressure (Petrie et al., 2024). Inflammatory markers also showed a downward trend. The level of C-reactive protein after 52 weeks was 0.76 mg/L in the semaglutide group and 0.84 mg/L in the placebo group. This corresponds to a reduction of 24% and 16%, respectively. It is confirmed that the inflammation damaging the endothelium is weakening (Verma et al., 2024; Thomas et al., 2026).

As part of STEP HFpEF, echocardiographic and cardiac magnetic resonance (CMR) substudies were performed. They indicated that some of the adverse structural features of obesity-related HFpEF can be partially reversed. Semaglutide slowed the process of enlargement of the left atrium. The mean difference in its volume after one year of active treatment was 6.13 mL (95% CI: -9.85 to -2.41; $p = 0.0013$). Parameters indicating improvement in the diastolic function of the heart were also noticeable. E wave velocity, the E/A ratio, and E/e' all decreased. The mean difference for E/e' reached -0.79 (95% CI -1.60 to 0.01; $p \approx 0.05$). It reflects lower pulmonary capillary wedge pressures and better myocardial relaxation (Solomon et al., 2024).

Prophylaxis of left atrial enlargement and its volume results in reduced pressure within the lungs. This has an effect on the functionality of the right ventricle in addition to enhancing the RV-pulmonary arterial coupling, as proven through imaging studies and meta-analyses (Musa et al., 2026; Solomon et al., 2024; Siddiqui et al., 2025).

Can dual GIP/GLP-1 agonism improve outcomes in HFpEF - The SUMMIT trial

731 people with HFpEF, obesity, and exercise-related dyspnoea were enrolled in the SUMMIT trial. The initial strong evidence provided was that this dual mechanism can improve their prognosis (Zile et al., 2025). Participants received 2.5 mg of tirzepatide as a weekly subcutaneous injection. In contrast to the STEP-HFpEF program, SUMMIT had a primary endpoint focused on time to cardiovascular death or worsening heart failure needing urgent intervention. Compared to placebo (HR roughly 0.62), tirzepatide cut the risk of this combined outcome by 38%. The decreased number of episodes of acute decompensation was mostly responsible. Functional capability was additionally improved more than with selective GLP-1 RA. Compared to placebo, patients getting tirzepatide had a mean KCCQ score rise of 6.9 points (95% CI 3.3–10.6; $p<0.001$) and a 6-minute walk test distance increase of 18.3 meters (95% CI 9.9–26.7; $p<0.001$) (Zile et al., 2025).

Cardiac magnetic resonance revealed that 1 year of therapy reduced the volume of EAT by nearly 25% (Kramer et al., 2025). Reducing epicardial fat lowers the heart's mechanical load and weakens the damaging paracrine effect of adipokines (pro-inflammatory). This is consistent with the changes detected in diastolic parameters and pulmonary pressures (Verma et al., 2024; Borlaug et al., 2023).

Studies show that GLP-1 receptor agonists and dual GIP/GLP-1 agonists have the ability to lower the chance of repeat heart failure events in individuals who have obesity and HFpEF. Data from trials of selective GLP-1 receptor agonists and tirzepatide combined suggest a 30-40% reduced risk of hospitalization for heart failure or composite cardiovascular death and heart failure (Musa et al., 2026). High-risk populations such as those suffering from type 2 diabetes, obesity, and chronic kidney disease may benefit from this treatment. The risk of developing heart failure can be reduced by almost a quarter (Borlaug et al., 2025). Key findings from major incretin-based HFpEF trials are summarized in Table 1.

Table 1. Summary of key characteristics and clinical outcomes of major incretin-based trials in obesity-related HFpEF.

Study (Author, Year)	Methodology & Sample (N)	Key Findings	Main Conclusion
STEP-HFpEF (Kosiborod et al., 2023a)	RCT; HFpEF (LVEF ≥45%), BMI ≥30, no DM (N=529)	Semaglutide increased KCCQ score versus placebo, was associated with greater weight loss, improved 6-minute walk distance, reduced NT-proBNP, and fewer heart failure events.	Improves symptoms, functional capacity, and congestion in obese HFpEF.
STEP-HFpEF DM (Borlaug et al., 2025)	RCT; HFpEF + T2D, BMI ≥30 (N=616)	Semaglutide increased KCCQ score and exercise capacity versus placebo, reduced body weight, with ~40% of functional improvement attributable to weight loss.	Benefits extend to patients with type 2 diabetes and are partly independent of weight reduction.
Pooled STEP-HFpEF (Butler et al., 2024)	Pooled RCT analysis (N=1145)	Semaglutide reduced worsening heart failure events, decreased need for diuretic escalation, and increased likelihood of diuretic reduction or discontinuation.	Suggests disease-modifying effects in obesity-related HFpEF.
STEP-HFpEF imaging substudy (Solomon et al., 2024; Petrie et al., 2024)	Imaging substudy; HFpEF subgroups	Semaglutide was associated with reduced left atrial volume, improved diastolic function parameters, and lower NT-proBNP levels.	Indicates reverse cardiac remodeling and improved filling pressures.
SUMMIT (Zile et al., 2025)	RCT; HFpEF (LVEF ≥50%), BMI ≥30 (N=731), median 104 wks	Tirzepatide reduced risk of cardiovascular death or worsening heart failure, improved KCCQ score and exercise capacity, and reduced body weight.	Demonstrates improved clinical outcomes with dual GIP/GLP-1 receptor agonism in HFpEF.
SUMMIT CMR substudy (Kramer et al., 2025)	CMR substudy; HFpEF subgroup	Tirzepatide reduced epicardial adipose tissue by ~25% after one year of treatment.	Epicardial fat reduction may contribute to clinical and functional benefits.

Incretin drugs and SGLT2 inhibitors

The basis of therapy in HFpEF is flozins, i.e., sodium-glucose cotransporter 2 (SGLT2) inhibitors. They act together with incretin-based drugs in their effect (Patel et al., 2024; Cimino et al., 2024). Their main role is improving hemodynamics by reducing preload on the heart. This is the result of glucosuria and osmotic diuresis, which leads to a reduction in intravascular volume. At the same time, the sympathetic nervous system is not strongly activated (Cimino et al., 2024). Incretins add a broader effect: they diminish inflammation, lower epicardial adipose tissue volume, improve vascular elasticity and endothelial function, and promote visceral fat loss (Roy et al., 2026; Cimino et al., 2024).

In comparison with flozin monotherapy, the combination of an SGLT2 inhibitor and a GLP-1 RA in patients with obesity, HFpEF, and type 2 diabetes lowers the risk of heart failure worsening, new atrial arrhythmias, and acute kidney injury (Yepes-Cortés et al., 2025; Neves et al., 2023). Together, these drugs act on two main mechanisms of obesity-related HFpEF: volume overload and chronic inflammatory-metabolic remodeling of the heart and blood vessels. Importantly, this does not cause excessive hypovolemia (Patel et al., 2024).

Limitations of therapy

Incretin drugs are not without drawbacks in clinical practice. Patients are discontinuing therapy mainly due to gastrointestinal problems such as nausea, vomiting, and delayed stomach emptying. Such symptoms are particularly pronounced at the beginning of treatment during dose escalation (Refaeli et al., 2025). Especially patients who have congestive heart failure experience exacerbated symptoms of dehydration. It may lead to acute kidney injury. The risk is even higher when loop diuretics are used at the same time (Dong & Sun, 2022). An increase in heart rate by about 1-5 beats per minute has been noted following therapy with GLP-1 analogs. In

cases where patients cannot tolerate an increase in heart rate, it would be advisable to consider the use of a beta blocker (Lubberding et al., 2024).

As part of the incretin therapy, there tends to be a rapid loss of weight among the patients. Sarcopenic obesity can arise in such circumstances. Apart from the reduction in adipose tissue, there will also be a reduction in lean body mass, particularly skeletal muscle. Older patients, most likely with frailty and myopathy, will experience high mortality and poor quality of life. With the rapid loss of lean body mass, there will be a reduced muscle pump in the periphery, reduced exercise capacity, and even dyspnoea. To limit this risk, resistance exercise training and higher dietary protein intake are recommended (Chen & Batsis, 2025).

After discontinuation of incretin therapy, there is a possibility of recurrence of inflammation and obesity. Therefore, treatment should be long-term, which creates a financial burden for some patients as well as for the healthcare system.

4. CONCLUSION

The HFpEF linked to obesity should be seen as a distinct clinical entity. Ectopic adipose tissue and persistent inflammation in these patients result in diastolic dysfunction, exercise intolerance, and a delayed diuretic response. It is now clear that combined GIP/GLP-1 agonists and GLP-1 receptor agonists can be utilized for non-weight loss objectives. These drugs reduce fibrotic cardiac remodeling, limit lipotoxicity, and improve endothelial nitric oxide synthesis. As a result, hsCRP and NT-proBNP levels decrease, left ventricular mass is reduced, and the amount of epicardial fat decreases. Patients also cover longer distances in the 6-minute walk test and achieve better scores on the KCCQ-CSS scale. The SUMMIT study additionally showed that tirzepatide reduced the combined risk of cardiovascular death and worsening heart failure.

When paired with the growing proof of a synergistic interaction between incretin medications and SGLT2 inhibitors, the case for a therapeutic transformation gets stronger. From an adjunct choice, incretin-based pharmacotherapy is becoming a major component of disease-modifying therapy in obesity-related HFpEF, one that targets the metabolic and inflammatory substrate of the syndrome rather than its hemodynamic surface. Still unanswered queries remain. More research is needed on the best order and mix of these substances. More study is required to ascertain long-term safety and cost-effectiveness. Improving patient selection is vital to maximize benefits and reduce risks like sarcopenia and treatment discontinuation.

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Informed consent

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Data and materials availability

All data associated with this study will be available based on the reasonable request to corresponding author.

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